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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/594,339	NAKAMURA ET AL.	
	Examiner	Art Unit	
	SHERIDAN SWOPE	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27,29 and 33-46* is/are pending in the application.

4a) Of the above claim(s) *3-27,29,33,34 and 36-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0906;0907*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of Invention I and SEQ ID NO: 6 in their response of June 9, 2008 is acknowledged. The elected invention is directed to the polypeptide of SEQ ID NO: 6 and variants thereof having at least 90% identity. It is noted that the mouse protein of SEQ ID NO: 10 is identical to SEQ ID NO: 6, while the rat protein of SEQ ID NO: 14 has 96% identity with SEQ ID NO: 6. Therefore, SEQ ID NO: 10 and 14, as recited by Claim 2, are encompassed by the elected invention.

Applicant's traversal is based on the argument that Groups II-VII, X, XII and XIII, especially Group II, should be examined simultaneously with Group I because said groups are so linked as to form a single general inventive concept under PCT Rule 13.1; sharing a special technical feature of cleaving DANCE with DANCE-specific protease. This argument is not found to be persuasive for the following reason. For a technical feature to be a special technical feature providing unity of invention, the technical feature must encompass all claims, not a subset of claims. The technical feature of cleaving DANCE with DANCE-specific protease is not shared by all claims. The restriction requirement is still deemed proper and is therefore made FINAL.

Claims 1-27, 29, and 33-46 are pending. Claims 3-27, 29, 33, 34, and 36-46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claims 1, 2, and 35 are hereby examined.

Priority

The priority date granted for Claims 1 and 35 is March 4, 2005, the filing date of PCT/JP05/04274, which disclosed polypeptides having at least 90% identity with SEQ ID NO: 6 and having integrin-binding activity. The priority date granted for Claim 2 is March 29, 2004, the filing date of JP 2004-096685, which disclosed the polypeptides of SEQ ID NO: 6, 10, and 14. If Applicants wish to perfect the claim to priority to JP 2004-096685, and English translation thereof should be submitted.

Information Disclosure Statement

The Information Disclosure Statement filed September 17, 2007 fails to comply with 37 CFR 1.98(a)(1)(ii)(b)(5) which requires that: "Each publication listed in an information disclosure statement must be identified by publisher, author (if any), title, relevant pages of the publication, date, and place of publication." Said information disclosure statement has been placed in the application file, but the information referred to therein has not been considered. If Applicants wish for the references therein to be considered, a supplemental Information Disclosure Statement should be submitted. Any subsequent rejection, based on consideration of the supplemental Information Disclosure Statement, will not be considered new grounds for rejection.

Abstract-Objections

The abstract is objected to. The application comprises two abstracts, filed on the same day, that are not identical. It is unclear which abstract is to be used. In addition, it appears that both abstracts are too long. MPEP 608.01(b) states:

> The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not

> exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 2, and 35 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The recited polypeptides are likely to occur in nature. Therefore, the claims fail to show the "hand of man". It is suggested that in Claim 1, the phrase "A polypeptide" be amended to "An isolated [or recombinant] polypeptide".

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reasons.

Claim 2 is rendered indefinite for improper antecedent usage. For Claim 2, the phrase "A polypeptide of claim 1" should be corrected to "The polypeptide of claim 1".

For Claim 35, the phrase "derived from" renders the claim indefinite. It is unclear whether said phrase means the polypeptide is a human or mouse protein, is a fragment of a human or mouse proteins, or is derived from a human or mouse protein. The latter would encompass all variants of a human or mouse protein. The skilled artisan would not know the

metes and bounds of the recited invention. For purposes of examination, it is assumed that said phrase means the polypeptide is a fragment of a human or mouse protein.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1, 2, and 35 are rejected under 35 U.S.C. 112, first paragraph, for lack of enablement. The prior art is enabling for the polypeptide consisting of residues 26-68 of human fibulin-5, which binds integrins αvβ3, αvβ5, and α9β1 (Nakamura et al, 2002, Fig 5; IDS). However, neither the specification nor the prior art provides enablement for any polypeptide having at least 90% identity with an amino acid of SEQ ID NO: 6 and having any integrin-binding activity or homo-complex formation activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In regards to this enablement rejection, the application disclosure and claims are compared per the factors indicated in the decision In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the art; (4) the amount of direction or guidance presented; (5) the presence or

absence of working examples; (6) the quantity of experimentation necessary; (7) the relative skill of those skilled in the art. Each factor is here addressed on the basis of a comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

Claims 1, 2, and 35 are so broad as to encompass any polypeptide having at least 90% identity with an amino acid of SEQ ID NO: 6 and having integrin-binding activity or homo-complex formation activity. It is noted that the phrase "an amino acid sequence of SEQ ID NO: 6" encompasses sequences as small as a dipeptide derived from SEQ ID NO: 6. The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claim. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired integrin-binding or homo-complex formation activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However in this case, the prior art is limited to the polypeptide consisting of residues 26-68 of human fibulin-5, which binds integrins $\alpha v\beta 3$, $\alpha v\beta 5$, and $\alpha 9\beta 1$.

While recombinant and mutagenesis techniques as well as some integrin binding assays are known, it is not routine in the art to screen for multiple substitutions or multiple modifications of SEQ ID NO: 6 and test all said modified polypeptides for binding to any integrin, as encompassed by the instant claims. Furthermore, the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success

in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable (Galye et al, 1993; Whisstock et al, 2003). In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of Claims 1, 2, and 35, which encompasses all polypeptides having at least 90% identity with an amino acid sequence of SEQ ID NO: 6 and having any integrin-binding activity or homo-complex formation activity. The specification does not support the broad scope of Claims 1, 2, and 35 because the specification does not establish: (A) the identity of any polypeptide having integrin-binding activity; (B) the utility of any polypeptide having homo-complex formation activity; (C) which integrins are bound by the recited polypeptides; (D) how any polypeptide having integrin-binding activity or homo-complex formation may, or may not, be modified without affecting the desired activity; (E) the general tolerance of the integrin-binding or homo-complex formation activity to modification and extent of such tolerance; (F) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function; and (G) the specification provides insufficient guidance as to which of the essentially infinite possible choices of polypeptides is likely to successfully bind to any known or unknown integrin, including recombinant variants.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of polypeptides with an large number of amino acid modifications of polypeptides having at least 90% identity with an amino acid sequence of SEQ

ID NO: 6 and having any integrin-binding activity or homo-complex formation activity. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Written Description

Claims 1, 2, and 35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of polypeptides having at least 90% identity with an amino acid sequence of SEQ ID NO: 6 and having any integrin-binding activity or homo-complex formation activity. The specification teaches the structure of no representative polypeptides that have integrin-binding activity and only a single representative species of such polypeptides having homo-complex formation activity. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of having any integrin-binding activity or homo-complex formation activity. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kowal et al, 1999. Claims 1, 2, and 35 recite a polypeptide having "an" amino acid sequence of SEQ ID NO: 6, 10, or 14. Said recitation encompasses sequences as small as a dipeptide. Kowal et al teach the rat ortholog of Dance and that, residues 26-68 thereof is an EGF-like repeat (Fig 1). Said EGF-like repeat of rat Dance has 97% identity with residues 4-45 of SEQ ID NO: 6 herein (see enclosed alignment). Kowal et al do not teach a peptide consisting of residues 26-68 of rat Dance. However, based on the teachings of Kowal et al, it would have been obvious to a person of ordinary skill in the art to make said peptide. Motivation to do so is provided by Kowal et al, wherein they teach that said EGF-like repeat comprises six consensus Ca^{2+}-binding cysteine residues an RDG motif and, thus, said EGF-like repeat is, more likely than not, an integrin binding domain (pg 1168, parg 4; Fig 1). Therefore, the skilled artisan would be motivated to make the peptide consisting of the EGF-like repeat, residues 26-68 of rat Dance, and test said peptide for integrin binding. The expectation of success is high, as the making of peptides and the use of peptides in binding assays is known in the art. Therefore, Claims 1, 2, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kowal et al, 1999.

Allowable Subject Matter

No claims are allowable.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages. It is also requested that the serial number of the application and date of amendment be referenced on every page of the response.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SHERIDAN SWOPE/
Primary Examiner, Art Unit 1652